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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,580	03/29/2007	Shyam S. Mohapatra	USF.208TCXC1	6999

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
01/20/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,580	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	RICHARD SCHNIZER	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *12 and 44-46* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *12 and 44-46* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/2/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/2/2011 has been entered.

Claim 46 was added.

Claims 12 and 44-46 are pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-14, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al (US Patent 5,693,532, previously cited), Tuschl et al (US 20040259247 A1, previously cited), Oliver (US 7425618, newly cited), Jin et al (Virology 273: 210-218, 2000, newly cited, but of record, reference R42 in the IDS of

8/5/08), Bitko et al (BMC Microbiology I:34, 2001, newly cited, but of record, reference R1 in the IDS of 4/17/09), and Chen et al (US 20040242518, previously cited).

McSwiggen taught methods of inhibiting the replication of RSV in vivo in infected humans through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. In one embodiment, the ribozymes are targeted to NS1 transcripts. See columns 2-3, for example (e.g. paragraph bridging columns 2 and 3). Preferred administration is by aerosol inhalation which would provide delivery to the airways (see column 9, lines 8-16). The ribozymes can be expressed from plasmid vectors (column 5, lines 10-12 and 27-52) under the control of eukaryotic pol I, pol II, or pol III promoters (column 9, lines 17-27).

McSwiggen did not teach administration of siRNA encoding vectors, or administration to a subject not suffering from RSV infection (instant claim 14).

Oliver taught methods of preventing RSV infection by administration of antibodies directed to RSV, and suggested that suggested that RSV infection could be prevented, managed, treated, or ameliorated through the use of antisense nucleotide sequences or RNA interference in combination with the anti-RSV antibodies. Column 29, lines 29-57, e.g. at lines 52-54.

Tuschl taught methods and materials for making and using short, double stranded interfering RNAs (siRNAs) against virtually any known gene for both research and clinical use. It is said the target gene to which the RNA molecule of the invention is directed may be a viral gene associated with a pathological condition (paragraph 30).

The siRNAs consist of sense and antisense strands of between 19 and 25 nucleotides in length, wherein the antisense strand is complementary to a target gene (cols. 1-3). Tuschl taught and/or suggested both in vitro transfection and in vivo delivery of siRNAs for therapeutic purposes (pages 3-4, and see examples). Thus, Tuschl provided a general blueprint for the design, synthesis, and application of short interfering RNAs.

Tuschl also directly compared and contrast ribozyme and RNAi technologies, stating at paragraph 148 that "...siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments."

Bitko demonstrated that RSV gene expression could be silenced through the use of siRNA in cell culture, and concluded that synthetic inhibitory dsRNAs are effective in specific silencing of RNA genomes that are exclusively cytoplasmic and transcribed by RNA-dependent RNA polymerases.

Jin showed that deletion of RSV NS1 served to attenuate viral replication in vitro and in vivo, see abstract.

Chen taught the use of siRNA expression vectors to inhibit viral infection in human lungs. Chen exemplified the use of siRNA expression vectors to prophylactically inhibit influenza infection in mouse lung. DNA expression vectors encoding siRNA directed to influenza virus transcripts were administered to mice, followed by administration of PR8 influenza virus. Fig. 26 shows that lower virus titers were observed when mice were given plasmid DNA that expressed either NP-1496a shRNA

or PB1-2257 shRNA. The virus titers were more significantly decreased when mice were given both influenza-specific plasmid DNAs together, one expressing NP-1496a shRNA and the other expressing PB1-2257 shRNA. These results show that shRNA expressed from DNA vectors can be processed into siRNA to inhibit influenza virus production in vivo, and that expression can be maintained for a sufficiently long period of time to achieve a prophylactic effect, i.e. to inhibit infection by viruses subsequent to administration of the expression vectors. See paragraphs 58, 185, 214, and Example 14 at paragraphs 429-437. Chen also taught that viral vectors could be used to deliver siRNAs (paragraphs 9, 55, 91, 161-164, 252. Chen envisioned delivery to humans (paragraphs 88, 156, and 248).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute siRNAs directed against RSV N1 for the N1-directed ribozymes of McSwiggen in order to inhibit the expression of an RSV mRNA, and to use the vectors of Chen to express them in the human lung in vivo. One of skill would have been motivated to do so because Oliver suggested the use of RNA interference for preventing RSV infection and because Tuschl taught that siRNAs were in general significantly more potent than ribozymes. Moreover, Bitko demonstrated that RSV gene expression was susceptible to inhibition by RNA interference, and Jin showed that the NS-1 gene product contributed to viral replication, providing further motivation to target NS-1 with siRNA.

In view of the fact that Chen demonstrated that siRNA expression vectors targeting influenza virus could be delivered to the mouse lung in vivo and reduce the

titre of the target virus, one of skill would have reasonably expected that siRNAs targeted to RSV could be successfully delivered and expressed in vivo as well. In view of the results of Bitko, one would have had a reasonable expectation that RSV RNAs could be successfully attacked by siRNAs, and so would have had a reasonable expectation of successfully inhibiting RSV NS1 expression and RSV replication, leading to a reduction in viral titer and an alleviation of symptoms. Moreover, since Chen showed that the expression vectors could be used prophylactically, one of ordinary skill would have surmised that expression of the siRNAs could be maintained for a period of time sufficient to inhibit viral replication that occurred after administration of the vectors, or that the expressed siRNAs had sufficient intracellular stability to inhibit viral replication that occurred after administration of the vectors. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to administer the siRNA expression vectors to a subject not suffering from RSV infection in order to prevent infection, and would have had a reasonable expectation of success in view of the results of Chen, Bitko, and Jin. It is noted that a RSV NS1 expression is considered to be a symptom of RSV infection, thus one of ordinary skill would have expected to achieve alleviation of that symptom in practicing the method of McSwiggen as modified above.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 5/2/2011 have been fully considered but they are not persuasive.

Applicant argues that the McSwiggen, Tuschl, and Chen references when combined would not yield predictable results. Applicant asserts that not all respiratory infections are the same and that the influenza infection of Chen is not the equivalent of RSV infection. Moreover, the cited references provide no empirical data to demonstrate that NS-1 targeting ribozymes or siRNAs can be prophylactically delivered to airway cells in vivo such that RSV gene expression can be inhibited, and in the absence of such empirical data there is no reasonable expectation of success.

The Office agrees that RSV and influenza are different, however the Chen reference is relied on to show that siRNA expression vectors can provide siRNA for a sufficient time after treatment such that siRNAs are available at a later time when a given virus may effect, and therefore have the potential to provide prophylactic benefit. The evidence of Bitko shows that RSV gene expression is susceptible to inhibition by RNA interference, i.e. that there do not appear to be any RSV-specific issues with employing RNA interference to inhibit RSV gene expression. Moreover, it was well known in the art that RNA interference agents expressed from vectors in a cell nuclease were effectively transported to the cell cytoplasm (the site of RSV gene expression) such that they are available for RNA interference. See e.g. Paddison et al (Genes Dev. 16: 948-958, 2002) at pages 952-954 which shows that shRNA transcribed from plasmid (nuclear) platforms is transferred to the cytoplasm where it is a substrate for

Dicer (a cytoplasmic enzyme) and functions to promote RNA silencing (see especially paragraph bridging columns on page 954). Thus one of ordinary skill was aware of suggestions to target RSV NS1 for inhibition (McSwiggen), was aware of suggestion to use siRNA to inhibit RSV gene expression (Oliver) and that a lack of NS1 expression resulted in RSV attenuation (Jin), knew how to make siRNAs and shRNAs against any target sequence (Tuschl and Chen), understood that RNA interference was thought to be more effective than ribozyme inhibition (Tuschl), understood that RSV gene expression could be inhibited by RNA interference (Bitko), and that shRNA-expressing vectors could be delivered to lung cells and could provide RNA interference functions after the time of delivery, i.e. at a later time when viruses might infect the cells (Chen). Accordingly one of ordinary skill had a reasonable expectation of successfully inhibiting RSV NS1 gene expression by administering to a subject a vector encoding an siRNA directed to NS1 mRNA, wherein the subject did not have an RSV infection at the time of administration.

At pages 5 and 6 of the response, Applicant addresses the issue of whether or not prior art knowledge of the relationship between NS1 and the cellular interferon response in vitro conferred a reasonable expectation that inhibiting NS1 would reduce RSV titer in vivo. Applicant argues, essentially, that in vitro data may not be relevant in vivo, and the issue was unpredictable in the absence of empirical in vivo data. Applicant also notes that not all of the cells in the host's respiratory system that mediate the interferon response are infected by RSV. Applicant's argument is unpersuasive because it does not provide any specific reason to expect that the results observed in

vitro would not be obtained in vivo. There is no clear reason to expect that the host's respiratory cells transfected with siRNA expression vectors and subsequently infected by RSV would not function similarly to those in vitro. Moreover, the issue of the relationship between NS1 and the interferon response appears moot in view of the new ground of rejection set forth above which demonstrates that the prior art provided a reasonable expectation that one of ordinary skill could have successfully inhibited RSV gene expression with prophylactic delivery of an expression vector encoding RSV NS1 siRNA to airway cells in a subject.

Applicant argues at pages 6-8 of the response that the Zhang (2005) reference (of record) provides evidence of unexpected results. This is unpersuasive because the results relied on by Applicant were obtained using a chitosan derivative (NG042) to formulate the siRNAs. The Zhang reference states that NG042 provided higher transduction efficiency and induces less inflammation compared to classical high molecular weight chitosan (page 60, right column, second and third sentences of paragraph bridging pages 60 and 61). The instant claims are not limited to the use of NG042, and it is unclear that the same results relied on as evidence of nonobviousness would be obtained without the use of NG042. Therefore the claims are not commensurate in scope with the evidence relied upon by applicant to establish non-obviousness. See MPEP 716.02(d).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Heather Calamita, can be reached at (571) 272-2876. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Richard Schnizer/
Primary Examiner, Art Unit 1635